

Attorney's Docket: 1999DE304
Serial No.: 09/914,478
Art Unit 1623

REMARKS

Applicants note that the rejection under 35 USC § 112 as being indefinite, has been removed.

Claims 1-10 and 12 stand finally rejected under 35 USC § 103(a) as being obvious from Balkovec '753 in view of Miyaura and Henle. Applicants traverse this rejection.

Applicant's invention is directed to an improved synthesis for terphenyl compounds. The main reference that the office bases its rejection on is Balkovec '753 the US equivalent of the WO 94/25050, which was discussed, extensively Applicants' patent application. On pages 1 and 2 of the US application Applicants state:

WO 94/25050 describes a multistage method for producing 4"-n-pentoxy[1,1':4',1'']-terphenyl-4-carboxylic acid (cf. pages 28 and 29 part A, part B and part C).

In a first step, 4'-bromo-4-hydroxybiphenyl is reacted with an n-pentyl halide to give the corresponding 4'-bromo-4-n-pentoxybiphenyl. The 4'-bromo-4-n-pentoxybiphenyl is reacted in a second step with n-butyllithium at -78°C to form, by transmetallation, 4'-lithium-4n-pentoxybiphenyl which, in another step likewise at -78°C, is reacted with triisopropyl borate. Hydrolysis and work-up result in 4'-n-pentoxybiphenyl-4-boronic acid, which is reacted in further steps with 4-iodobenzoic acid in a standard Suzuki coupling. The 4"-n-pentoxy[1, 1':4', 1'']-terphenyl-4-carboxylic acid is obtained as crude product which is purified by chromatography on silica gel.

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WO 94/25050 states yields only for the stages (part A and part B) up to formation of 4-(4-n-pentyloxyphenyl)phenylboronic acid. There is no statement of yield in part C, which relates to the production of 4"-n-pentoxyl[1,1':4',1'']-terphenyl-4-carboxylic acid.

Then on page 18 and 19 of the US Application sets forth:
Comparative examples according to WO 94/25050 for preparing 4"-n-pentoxyl[1,1':4',1'']-terphenyl-4-carboxylic acid

Comparative example 1

Preparation of 4'-n-pentoxylbiphenyl-4-boronic acid from 4-bromo-4'-n-pentoxylbiphenyl

31.9 g (0.1 mol) of 4-bromo-4'-n-pentoxylbiphenyl are dissolved in 640 ml of tetrahydrofuran under a nitrogen atmosphere and cooled to -78°C, and 67 ml (0.11 mol) of 15% strength solution of n-butyllithium in hexane are added dropwise over the course of 2 hours. During this, the internal temperature is kept in the range from -78°C to -65°C. After the addition is complete, the thick milky suspension stirred at -78°C for a further 15 minutes and then 25.5 ml (0.11 mol) of triisopropyl borate are added dropwise at -78°C over the course of 15 minutes. After the borate addition is complete, the resulting clear solution is stirred at -78°C for 15 minutes.

This is followed by a removal of the cooling bath and, after 40 minutes, the solution is adjusted to pH 2 with 100 ml of 2N hydrochloric acid. The phases are separated, the organic phase is washed with water and saturated brine and then the solvents are removed by distillation with 5 addition of 200 ml of water. The precipitated solid is filtered off and dried. 25.8 g

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(91%) of 4'-n-pentoxybiphenyl-4-boronic acid of melting point 148-150°C are obtained.

Comparative example 2

Preparation of 4"-pentoxy-[1,1':4',I"]-terphenyl-4-carboxylic acid from 4'-n-pentoxybiphenyl-4-boronic acid

25 g (0.088 mol) of 4'-n-pentoxybiphenyl-4-boronic acid and 21.8 g (0.088 mol) of 4-iodobenzoic acid are suspended under an inert gas atmosphere in a mixture of 270 ml of ethanol, 750 ml of toluene and 132 ml of a 2M sodium carbonate solution and, after addition of 5.08 g (4.4 mmol) of tetrakis(triphenylphosphine)palladium, heated under reflux for 18 hours. The gray-brown mixture is cooled, acidified and extracted with ethyl acetate. The organic phase is washed with water and saturated brine, dried

(sodium sulfate) and filtered through Celite. Removal of the solvent results in 1.2 g of a solid which, however, according to HPLC analysis (comparison with reference substance) contains no 4"-n-pentoxy [1,1':4',I"]-terphenyl-4-carboxylic acid at all.

Evidently, no 4-n-pentoxy-[1,1':4',I"]-terphenyl-4-carboxylic acid has been formed by the synthetic route indicated in WO 94/25050.

Unexpectedly, in view of the prior art, using the process of the present invention this compound can be prepared with good yields and high purity as set forth in the Application on pages 14-18:

Preparation of 4"-n-pentoxy-[1,1':4',I"]-terphenyl-4-carboxylic acid from 4-n-pentoxyphenylboronic esters

Example 5

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Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 129 g of glycol ester of 4-n-pentoxyphenyl boronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 350 mg of PdC12(PPh3)2 are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1 000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 141 g (78%) of 4"-n-pentoxy [1,1':4',1'']-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 6

Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid

32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of ethylene glycol and, while stirring vigorously, 70 mg of PdC12(PPh3)2 are added, and the mixture is stirred at 120°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 25.2 g (70%) of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid with a purity of > 99%.

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Example 7

Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid

32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of ethylene glycol and, while stirring vigorously, 18 mg of PdCl₂ and 26.6 mg of PPh₃ are added, and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 24.1 g (67%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 8

Preparation of 4"-n-pentoxy-[1, 1':4', 1"]-terphenyl-4-carboxylic acid

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 129 g of glycol ester of 4-n-pentoxyphenylboronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 17.5 ml of a Pd(dba)₂ solution are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1,000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at

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80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 132 g (73%) of 4"-n-pentoxy terphenyl-4-carboxylic acid with a purity of > 99%.

Preparation of the Pd(dba)₂ solution:

Under an inert gas, 1.47 g of sodium tetrachloropalladate are suspended in 175 ml of ethylene glycol and heated to 60°C and, after addition of 3.65 g of dibenzylidene acetone (dba), stirred at 60°C for 15 minutes. This is followed by addition of 7.5 g of sodium acetate and stirring at room temperature for a further 60 minutes. The dark-colored solution is employed as such.

Example 9

Preparation of 4"-n-pentoxy-[1,1':1'']- terphenyl-4-carboxylic acid

20.1 g of 4'-iodobiphenyl-4-carboxylic acid, 13.1 g of sodium carbonate and 21.4 g of glycol ester of 4-n-pentoxyphenylboronic acid are introduced into 260 g of dimethyl sulfoxide (DMSO) and, after addition of 160 mg of PdCl₂(PPh₃)₂, heated at 100-110°C for 2 hours. The solid is filtered off at 40°C, washed with dimethyl sulfoxide and suspended in 100 ml of water. It is then heated to 80°C, and 47 g of 37% strength sulfuric acid are added dropwise over the course of 1 hour. The mixture is stirred at 80°C for a further 30 minutes, cooled at 40°C and filtered. Drying and crystallization from dimethylacetamide results in 18 g (81%) of 4"-n-pentoxy-[1,1':4',1'']terphenyl-4-carboxylic acid with a purity of > 99%.

Example 10

Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid

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32.4 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 25.8 g of glycol ester of 4-n-pentoxyphenylboronic acid and 15.9 g of sodium carbonate into 300 ml of methanol/ethylene glycol 9:1 and, while stirring vigorously, 70 mg of $\text{PdCl}_2(\text{PPh}_3)_2$ are added, and the mixture is stirred under reflux for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 30 g of 37% strength sulfuric acid and 200 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 28.9 g (80%) of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid with a purity of > 99%.

Example 11

Preparation of 4"-n-pentoxy-[1,1':4',1"]-terphenyl-4-carboxylic acid

162 g of 4'-iodobiphenyl-4-carboxylic acid are introduced together with 155 g of 2,2-dimethylpropane-1,3-diol ester of 4-pentoxyphenylboronic acid and 79.5 g of sodium carbonate into 1.5 l of ethylene glycol and, while stirring vigorously, 350 mg of $\text{PdCl}_2(\text{PPh}_3)_2$ are added and the mixture is stirred at 80°C for 6 hours. The hot reaction mixture is cautiously poured into a mixture of 150 g of 37% strength sulfuric acid and 1000 g of water, and the mixture is heated at 90-100°C for 30 minutes. After filtration and washing with water, the crude product is dried at 80°C/100 mbar and then recrystallized from dimethylacetamide. This affords after drying 43.2 g (24%) of 4"-n-pentoxyterphenyl-4-carboxylic acid with a purity of > 99%.

Example 12

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Preparation of 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylic acid
from
4-n-pentoxyphenylboronic acid

34.1 g (0.1 mol) of 95% pure 4'-iodobiphenyl-4-carboxylic acid are introduced together with 26 g (0.125 mol) of 4-n-pentoxyphenyl boronic acid, 15.9 g (0.15 mol) of sodium carbonate and 70 mg of bis(triphenylphosphine)palladium dichloride ($\text{PdCl}_2(\text{PPh}_3)_2$) into 300 ml of DMSO. The suspension is stirred at 80°C for 6 hours, the solid is filtered off, introduced into water, acidified with 37% strength sulfuric acid, heated at 95°C for 30 minutes and filtered again. Recrystallization from dimethylformamide (DMF) results in 22.1 g (61%) of 4"-n-pentoxy-[1,1':4',1''] terphenyl-4-carboxylic acid.

Preparation of methyl
4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate from
methyl 4'-iodobiphenyl-4-carboxylate

Example 13
Preparation of methyl
4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate

33.8g (0.1 mol) of methyl 4'-iodobiphenyl-4-carboxylate are introduced together with 29.3 g (0.125 mol) of glycol ester of 4-n-pentoxyphenylboronic acid, 70 mg of bis(triphenylphosphine)palladium dichloride and 15.9 g (0.15 mol) of sodium carbonate into 300 ml of DMF and stirred at 80°C for 12 hours. After filtration and washing with water, the dried residue is recrystallized from DMF. This affords 20.5 g (45%) of methyl 4"-n-pentoxy-[1,1':4',1'']-terphenyl-4-carboxylate of melting point 248°C.

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Applicants note that WO 94/25050, the equivalent of Balkovec '753 had been discussed in the instant application as filed and on 2 of the application Applicants note:

WO 94/25050 states yields only for the stages (part A and part B) up to formation of 4-(4-n-pentyloxyphenyl)phenylboronic acid. There is no statement of yield in part C, which relates to the production of 4"-n-pentoxy[1,1':4',1"]-terphenyl-4-carboxylic acid.

In the specification Applicants ran a Comparative Examples 1 & 2 in accordance with WO 94/25050 and where not able to reproduce the results avered in this reference. **Based upon these showing contained in Applicants' specification the prior art does not provide a reasonable expectation of succeeding in what Applicants have done.** In light of Applicants comparative examples and the experimental data on Applicants process Applicants' respectfully request that the obvious rejection to USP 5,948,753 Balkovec, which was discussed throughout Applicants' application in its European form, as WO 94/25050, be withdrawn and the claims allowed.

Further, Applicants reiterate that the process described by Balkovic differs from the one of the present invention, in that the instant invention starts with a metallated phenylcompound which is reacted with a boronic acid ester, hydrolyzed and reacted with an alcohol or glycol to form pentoxyphenylboronic acid (or the anhydride or esters) and a diphenylcompound is subsequently added to give the terphenyl. While Balkovec starts with a brominated diphenyl compound which is reacted with butyllithium and the boronic acid ester to form th

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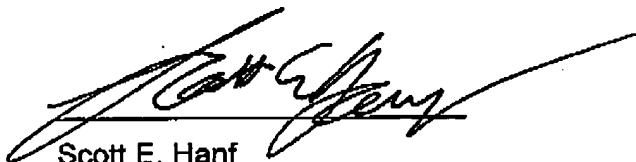
pentoxydiphenylboronic acid ester. Addition of 4-iodo-benzoic acid results in the terphenyl compounds.

The process of the instant invention is a completely new route, since the nucleophil and electrophil employed by Balkovec have been swapped. This results surprisingly in an increased selectivity and improved yields.

As the total number of claims does not exceed the number of claims originally paid for, no fee is believed due. However if an additional fee is required, the Commissioner is hereby authorized to credit any overpayment or charge any fee deficiency to Deposit Account No. 03-2060.

Reconsideration and allowance of this application is respectfully requested.

Respectfully submitted,



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